# Altered Innervation Pattern in Ligaments of Patients with Basal Thumb Arthritis

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## Abstract

**Purpose** The population of mechanoreceptors in patients with osteoarthritis (OA) lacks detailed characterization. In this study, we examined the distribution and type of mechanoreceptors of two principal ligaments in surgical subjects with OA of the first carpometacarpal joint (CMC1).

**Methods** We harvested two ligaments from the CMC1 of eleven subjects undergoing complete trapeziectomy and suspension arthroplasty: the anterior oblique (AOL) and dorsal radial ligament (DRL). Ligaments were divided into proximal and distal portions, paraffin-sectioned, and analyzed using immunoflourescent triple staining microscopy. We performed statistical analyses using the Wilcoxon Rank Sum test and ANOVA with post-hoc Bonferroni and Tamhane adjustments.

**Results** The most prevalent nerve endings in the AOL and DRL of subjects with OA were unclassifiable mechanoreceptors, which do not currently fit into a defined morphological scheme. These were found in 11/11 (100%) DRLs and 7/11 (63.6%) AOLs. No significant difference existed with respect to location within the ligament (proximal versus distal) of mechanoreceptors in OA subjects.

**Conclusion** The distribution and type of mechanoreceptors in cadavers with no to mild OA differ from those in surgical patients with OA. Where Ruffini endings predominate in cadavers with no to mild OA, unclassifiable corpuscles predominate in surgical patients with OA. These findings suggest an alteration of the mechanoreceptor population and distribution that accompanies the development of OA.

**Clinical Relevance** Identification of a unique type and distribution of mechanoreceptors in the CMC1 of symptomatic subjects provides preliminary evidence of altered proprioception in OA.

**Keywords**
- carpometacarpal
- innervation
- joint
- osteoarthritis
- proprioception
- trapeziometacarpal

The complex human thumb carpometacarpal joint (CMC1) is associated with a high prevalence of osteoarthritis (OA), especially in older women, and is the most common site of OA surgery in the upper extremity.[1] The unique concavo-convex shape of CMC1 provides stability with compressive forces, while its ligamentous apparatus retains the joint when subjected to tensile forces.[2] Intact proprioceptive mechanisms are critical for joint stability as previously



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demonstrated in the shoulder, knee, ankle, and wrist joints.[3–8] Impaired proprioceptive and neuromuscular functions have been proposed to be two of the underlying causes of OA development in other joints, such as the knee,[9–13] but this has yet to be evaluated in the CMC1 joint.

Mechanoreceptors play a central role in this process, detecting abnormal mechanical stress and providing afferent information on joint position and velocity. In addition, they provide signaling through inflammatory mediators, such as prostaglandins and cytokines, which are important elements of OA pain.[14,15] Ruffini endings are more common in non-weight bearing joints, representing low-threshold and slowly adapting mechanoreceptors.[16] Pacini corpuscles are more common in weight-bearing joints representing low-threshold, rapidly adapting mechanoreceptors.[14,17] Some receptors have been deemed "unclassifiable," meaning they cannot morphologically be classified as Pacini, Ruffini or free nerve endings.[14] Ruffini endings, Pacinian corpuscles and unclassifiable receptors have been observed in non-arthritic wrist, shoulder and ankle joints[16,18,19] but their role and occurrence is unclear in joints with OA, in particular the CMCI.

The distribution of mechanoreceptors corresponds to specific proprioceptive functions of the individual ligament, regardless of presence close to the bony insertion or even distribution throughout the ligament.[20,21] The distribution of the mechanoreceptors within the sub-regions of the ligament may vary,[20,22] which will impact its proprioceptive features. Previous studies have examined the innervation of CMC1 ligaments with absent or minimal signs of OA[23,24] and the histologic and innervation differences between principal CMC1 ligaments in surgical patients with OA.[25] The current study expands these findings by examining mechanoreceptor characteristics and distribution within these ligaments in specimens with advanced and symptomatic OA.

The aim of this study is to examine the innervation within two principal ligaments of CMC1: the anterior oblique (AOL) and dorsal radial ligament (DRL) in surgical subjects with OA. We hypothesize that the distribution and type of mechanoreceptors differ between thumbs with OA and those with no to mild OA. We sought to answer two questions: 1) Is there a difference in total mechanoreceptor distribution and 2) average proportion of each mechanoreceptor between the proximal and distal ends of the AOL and between the proximal and distal ends of the DRL? Differences between the distribution and type of mechanoreceptors found in cadavers with no to mild OA and surgical patients with OA may be an indication of symptomatic disease.

## Materials and Methods

### Study Design

This is a prospective cohort study of the mechanoreceptor population within the AOL and DRL ligaments of eleven surgical subjects. The study was performed in strict accordance with local ethical and practical protocols. The cohort consisted of ten female subjects and one male subject (six right and five left hands undergoing trapeziectomy and suspension arthroplasty with radiographic Eaton stage 2–4 OA[26] (►**Table 1**). An experienced hand surgeon performed trapeziectomy and ligament harvest, identifying the DRL and less prominent AOL under 3.5 loupe magnification.[23,27] A five mm width of ligament (AOL and DRL) was harvested at the insertion of both trapezium and metacarpal and suture-marked with 6–0 nylon at the distal insertion for orientation.

### Slide Preparation

Slides were prepared using the protocol established by Lee and colleagues.[24] Twenty-two ligaments were harvested and immediately fixed in 4% formaldehyde, embedded in paraffin, and sectioned at a thickness of five micrometers (μm) before being mounted on glass slides. Paraffin was removed from ligament specimens using serial xylene washes (3 × 3 minute) followed by gradual rehydration. A microwave antigen retrieval method was then used to expose antibody-binding sites. Specimens were permeabilized with 1% Triton-X100 and blocked with Image-iT FX (Invitrogen, Carlsbad, CA). Specimen samples were stained with primary antibodies for one hour at 37°C in a humid chamber, rinsed for three × five minutes in 0.1 mol/L phosphate-buffered solution (PBS), and stained with secondary antibodies under the same conditions. A final three × five-minute rinse in 0.1 mol/L PBS was performed before using ProLong Gold Anti-Fade Reagent with 4',6'- diamidino-2-phenylindole (DAPI) (Invitrogen) to mount the slides.

### Primary Antibodies

Rabbit anti-nerve growth factor receptor p75 (p75) (Code AB1554, Millipore, Billerica, Massachusetts) and rabbit anti-Protein Gene Product 9.5 (PGP9.5) (Code AB1761, Millipore, Billerica, Massachusetts) were the two primary antibodies used. This transmembrane protein is expressed on the cell membrane of nerve cells and responsible for signaling related to neuronal growth, migration, differentiation and cell death. p75 is considered the primary antibody in identification of the Pacini corpuscle as it marks the perineurial lamellar layers that are characteristic of this mechanoreceptor.[16] We optimized p75 to a dilution of 1:100 in 0.1 mol/L PBS in a volume of 100μL per ligament sample.

Rabbit monoclonal anti-Protein Gene Product (PGP) 9.5 (Code AB1761, Millipore, Billerica, MA) was also used. This

**Table 1** Baseline characteristics of surgical subjects with osteoarthritis of the first carpometacarpal joint

| Characteristic | n = 11 |
|---|---|
| Gender - % (n) | |
| Females | 90.9 (10) |
| Males | 9.1 (1) |
| Age - mean (range) | 67 (51, 83) |
| Hand -% (n) | |
| Right | 54.5 (6) |
| Left | 45.5 (5) |

antibody is directed against PGP9.5, a pan-neuronal marker present in neuronal cytoplasm in all mammals including humans, and especially in the metabolically dynamic regions of the cell. PGP9.5 is the primary antibody in identification of the afferent axons of mechanoreceptors and the bulbous terminals of the Ruffini endings.[16] We optimized anti-PGP9.5 to a dilution of 1:400 in 0.1 mol/L PBS in a volume of 100μL per ligament sample.

### Secondary Antibodies

Secondary antibodies included goat anti-rabbit Alexa Fluor 488 to emphasize p75 and goat anti-mouse Alexa Fluor 647 to emphasize PGP9.5 (Invitrogen, Carlsbad, California). We optimized this antibody to a dilution of 1:200 with 0.1 mol/L PBS in a volume of 100μL per ligament sample.

p75 and PGP9.5 in conjunction with ProLong Gold Anti-Fade Reagent with 49,69-diamidino-2- phenylindole (DAPI) (Invitrogen) is a validated triple-stain method for visualizing mechanoreceptors, nerves and arteries/arterioles in contrast with collagen within ligaments.[24] For control staining, the antibodies were stained on tissues with known neural content (cadaveric median nerve), confirming the specificity of the markers.

### Immunohistochemical Microscopy

A fluorescence microscope (Observer.Z1, Carl Zeiss Micro-Imaging, Thornwood, New York) was used to image the immunohistochemical sections. Wavelength settings of 358, 488, and 596 nm were used on multidimensional acquisition setting to analyze sensory nerve endings. Independent variables consisted of the type of ligaments (AOL versus DRL) as well as location on the ligaments (proximal versus distal insertion). Dependent variables consisted of the type of mechanoreceptors found on each type of ligament and in each location (Ruffini, Pacini Corpuscle, Unclassifiable Corpuscle, Free Nerve Endings).

### Analysis of Innervation

We analyzed four ligament samples from each of eleven patients. We performed semiquantitative analysis as follows: the ligaments were cut in half and two representative five μm sections were selected and analyzed from each of the two ligaments from the eleven specimens, one proximal and one distal to the ligament attachment (42 samples total). Two AOL samples were insubstantial both in length and caliber; we therefore sampled and analyzed only the distal portion. Adjacent five μm sections were also analyzed to increase specificity of nerve and mechanoreceptor identification. Two investigators independently viewed each specimen and final mechanoreceptor counts were averaged.

We employed a previously described ordinal grading system for analysis of ligament innervation, quantifying the degree of innervation and assessing mechanoreceptor presence.[16,28] For each sample, +++ (3.0) was used to indicate rich innervation with several nerve fascicles and mechanoreceptors, ++ (2.0) to indicate a single nerve fascicle and mechanoreceptor, + (1.0) to indicate nerve fascicle alone, and – (0.0) to indicate no signs of innervation.

### Statistical Methods

Data were analyzed using Statistical Analysis Software (SAS) Enterprise Guide Version 6.1 (Cary, North Carolina). Statistical tests had a two-tailed α of 0.05. Variables were graphically examined for normal distributions and assessed for outliers to determine the appropriate statistical test. For continuous variables the Shapiro-Wilk test statistic was used to assess normality.

The Wilcoxon Rank Sum test was used to estimate the pattern of innervation distribution between proximal and distal ends for both the DRL and AOL. Pairwise comparisons were made between the proximal and distal portion of each ligament producing p-values and 95% confidence limits based on the Hodges-Lehmann estimate for the mean differences between each ligament location.

To determine the general distribution of mechanoreceptors, irrespective of ligament type or location, the proportion of each mechanoreceptor type was averaged across all 42 specimens. The specific pattern of mechanoreceptor distribution between the distal and proximal portions of the AOL and DRL was determined by averaging total counts of each mechanoreceptor type based on ligament and location across all eleven subjects. ANOVA with post-hoc Bonferroni and Tamhane adjustments was used for each mechanoreceptor type (Ruffini ending, Pacini corpuscle, unclassifiable corpuscle, free nerve ending) for statistical hypothesis testing. A test of homogeneity of variances was performed to determine whether Bonferroni or Tamhane adjustments were used.

## Results

### Intra-Ligament Mechanoreceptor Distribution

We found no statistically significant mean difference between innervation of the distal and proximal DRL (median: 0.0, interquartile range: 0.0 to 0.5, Wilcoxon Rank Sum test, $p = 0.235$, 95% confidence limits (CL): 0.0 to 1.0) of OA surgical subjects (►**Fig. 1**). Similarly, we found no statistically significant mean difference between innervation of the distal and proximal AOL (mean: -0.045, standard deviation: 1.491, Wilcoxon Rank Sum test, $p = 0.907$, 95% CL: -1.0 to 1.5) of OA surgical subjects.

### Inter-Ligament Mechanoreceptor Distribution

#### General Distribution

On average, unclassifiable corpuscles were the most prevalent type of mechanoreceptor encountered in the distal and proximal portions of both the DRL and AOL (►**Fig. 2**).

#### Ruffini Ending

In our study, Ruffini endings sized 50–150 μm were identified with characteristic terminal dendritic branches, partial encapsulation of the receptor, and specific p75 and PGP9.5 immunofluorescence (IF) (►**Fig. 3**) We identified the greatest number of Ruffini endings in the distal DRL (7.5/11, $\mu = 0.68$ per specimen, $\sigma = 0.60$), followed by the proximal DRL (6/11,

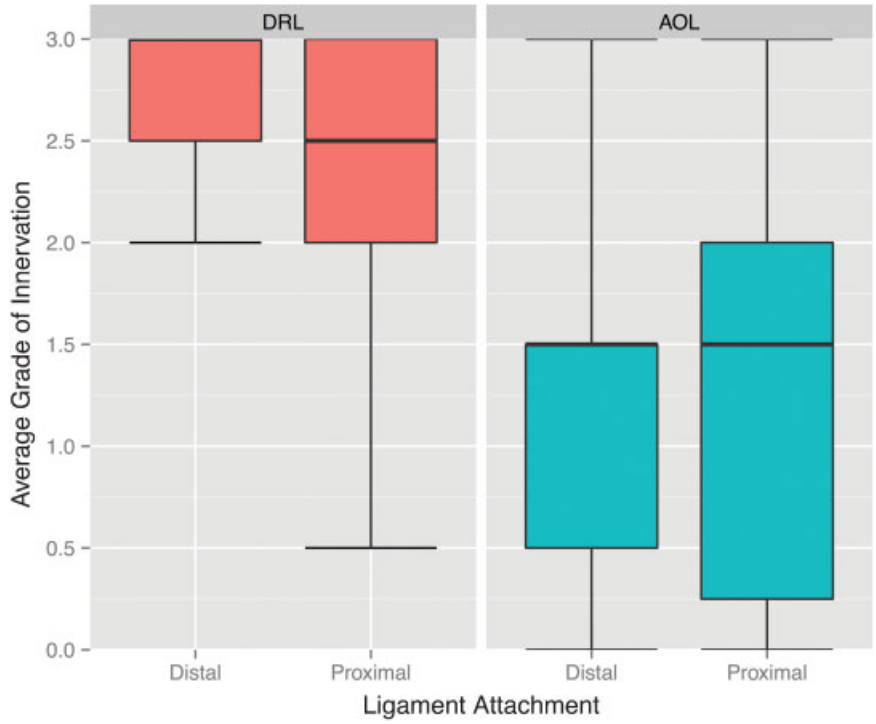


**Fig. 1 Mechanoreceptor Distribution within the AOL and DRL.** Semiquantitative distribution of sensory nerve endings and nerve fascicles in the distal and proximal portions of the dorsal radial and anterior oblique ligaments from 11 surgical CMC osteoarthritic patient specimens. For each sample, +++ (3.0) indicates richly innervated with several nerve fascicles and mechanoreceptors; ++ (2.0) indicates a single nerve fascicle and mechanoreceptor; + (1.0) indicates nerve fascicle alone; – (0.0) indicates no signs of innervation. Grading from two investigators was averaged.

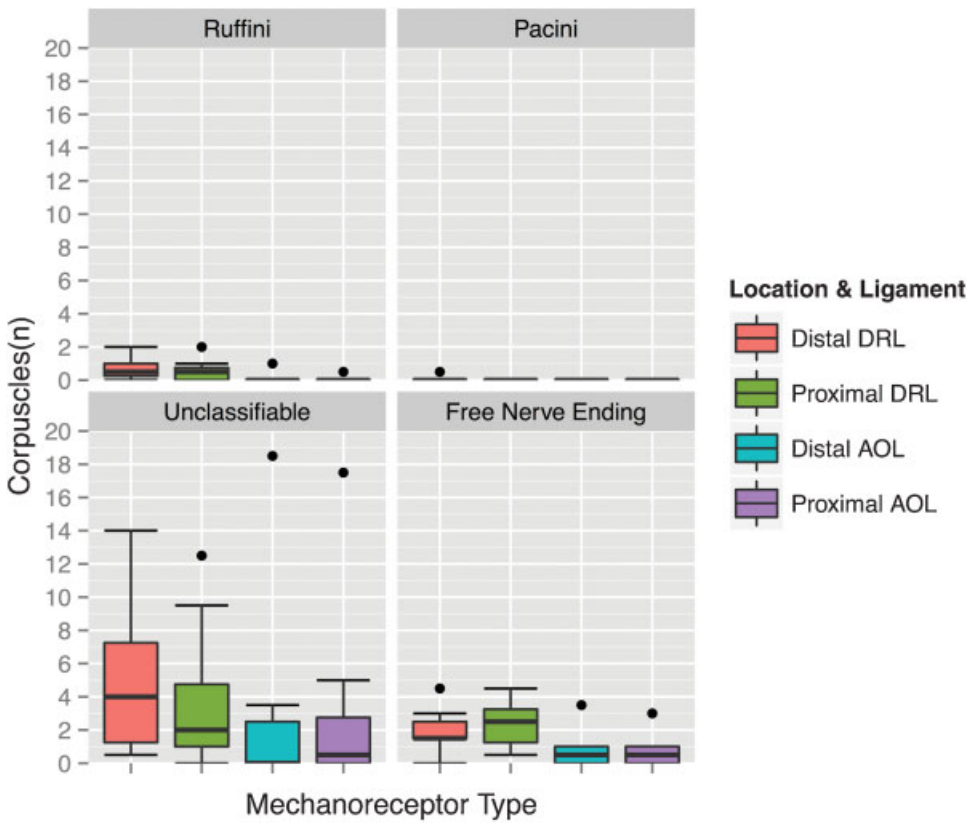


**Fig. 2 Average number of mechanoreceptor of each types on Proximal and Distal Ends of the AOL and DRL.** Significant difference only exists between average number of Ruffini Endings in samples of the distal DRL and proximal AOL ligaments.

$\mu$= 0.55 per specimen, $\sigma$ = 0.61), distal AOL (1/9, $\mu$ = 0.11 per specimen, $\sigma$ = 0.33) and proximal AOL (0.5/11, $\mu$ = 0.05 per specimen, $\sigma$ = 0.15) (►**Fig. 2**). A significant difference existed between the average number of Ruffini endings found in the distal DRL and proximal AOL (p = .039).

### Pacini Corpuscle

We identified one Pacini corpuscle in 42 samples of the eleven patients, located in the distal DRL (0.5/11, $\mu$ = 0.05 per specimen, $\sigma$ = 0.15). It was distinguishable by its onion-like, lamellar capsule with distinct p75 IF.

### Unclassifiable Corpuscles

We found an abundance of unclassifiable corpuscles in the distal and proximal DRL and AOL. Unclassifiable corpuscles are sensory corpuscles ~50µm in size, with a round/ovular appearance, variable capsular p75 and PGP 9.5 IF expression, and that can neither be defined as Ruffini, Pacini, nor free nerve endings (►**Fig. 4**). They often clustered together into bundles small corpuscles. They have similar morphology to one another and represent one type of unclassifiable mechanoreceptor. We observed a wide distribution of these corpuscles in all eleven DRLs and seven out of eleven AOLs. We did not find a significant difference in the average number of unclassifiable corpuscles in the distal DRL (54/11, $\mu$ = 4.91 per specimen, $\sigma$ = 4.31) and proximal DRL (39.5/11, $\mu$ = 3.59 per specimen, $\sigma$ = 4.13) and distal AOL (25/9, $\mu$ = 2.78 per specimen, $\sigma$ = 6.04) and proximal AOL (29.5/11, $\mu$ = 2.68 per specimen, $\sigma$ = 5.19), likely due to large variances in the number of corpuscles found (►**Fig. 2**). This was true whether the corpuscles were counted individually or in bundles.

### Free Nerve Endings

We commonly found free nerve endings adjacent to vessels and in connective tissue sheaths within ligaments. We observed free nerve endings in six of eleven DRLs and four out of eleven AOLs. We found a variance of 0 to 4.5 per specimen. We found no significant differences in the average number of free nerve endings in the distal DRL (21/11, $\mu$ = 1.91 per specimen, $\sigma$ = 1.18) and proximal DRL (26/11, $\mu$ = 2.36 per specimen, $\sigma$ = 1.32) and distal AOL (7.5/9, $\mu$ = 0.83 per specimen, $\sigma$ = 1.09) and proximal AOL (7/11, $\mu$ = 0.64 per specimen, $\sigma$ = 0.90) (►**Fig. 2**). This was true whether they were counted individually or in bundles.

## Discussion

We found that the distribution and type of mechanoreceptors in cadavers with no to mild OA[23,29] differ from those in surgical patients with advanced and symptomatic OA (►**Table 2**). Where Ruffini endings predominate in cadavers with no to mild OA, unclassifiable corpuscles predominate in surgical patients with OA. Additionally, we found unclassifiable receptors consistently dispersed over both the proximal and distal portion of the ligaments studied, with no preference for either end as in cadavers with no to mild OA.[23,29]

One potential explanation for this observation could be pathologic hyperplasia of unclassifiable receptors due to repetitive trauma or the participation of inflammatory mediators prior to or during OA development. This type of reactive phenomenon has been seen during Pacinian hyperplasia in the hand, often as a result of previous trauma, causing local pain.[30,31] Impaired proprioceptive characteristics of these ligaments may further aggravate OA[9] and may,

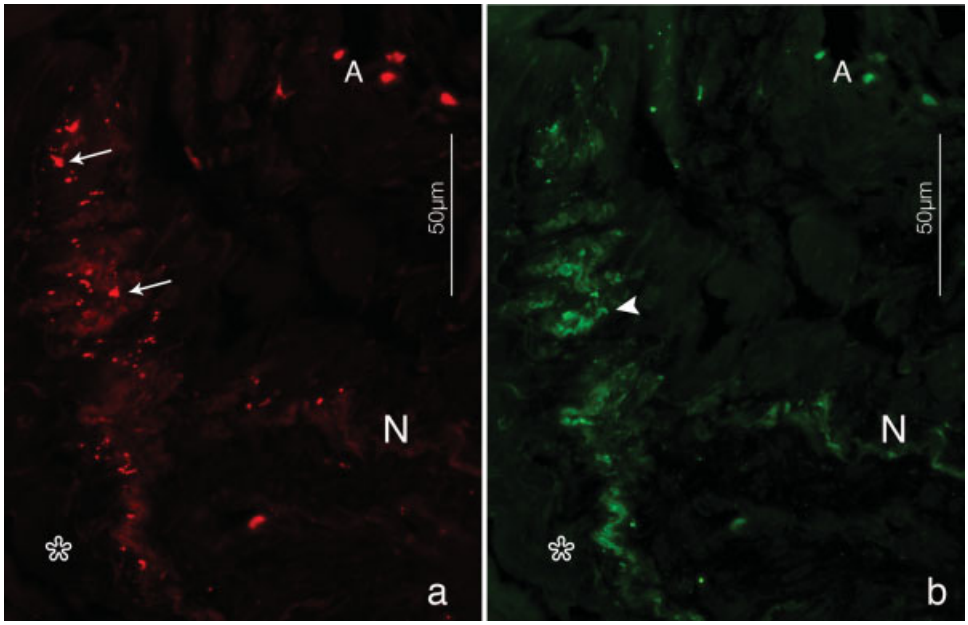


**Fig. 3** Ruffini ending from a dorsal radial ligament stained with **(a)** PGP9.5, a pan-neuronal marker present in neuronal cytoplasm illustrating the axons of the afferent parent axon (N) and the terminal bulbous ending of the Ruffini (*arrows*); and **(b)** p75 expressed on the cell membrane, indicating the perineurial layers of the nerve ending (*arrowhead*). A, arteriole; *, identical areas in both images.

**Fig. 4 Unclassifiable Corpuscles.** Two unclassifiable corpuscles (*arrowheads*) and a transversely cut arteriole(*) from an anterior oblique ligament stained with (a) p75 (b) PGP9.5 and (c) DAPI (blue). DAPI IF with staining of the nuclei of fibrocytes and smooth muscle cells distinguishes arterioles from unclassifiable corpuscles as the dense circular DAPI of the arterial wall and lumen illuminates the arteriole (*). Unclassifiable corpuscles are seen as small, rounded and partially encapsulated corpuscles that lack the Ruffini's dendritic endings as well as the Pacinian's p75 specific layers.

therefore, further stimulate pain pathways. Another plausible explanation of the occurrence of these unclassifiable receptors is that they are degenerated or damaged mechanoreceptors and formed as a part of the OA process. However, their exact function warrants further studies.

Free nerve endings were the second most common type of receptors found, followed by Ruffini endings and Pacini corpuscles. Free nerve endings likely play a significant role in OA pain generation, as they are mediators of inflammatory or noxious input.[32,33] Ruffini endings monitor joint position and dynamic changes in velocity and amplitude of the joint. In contrast to cadaver studies, these were not the predominant form of mechanoreceptor found in the ligaments of surgical patients with OA.[24] In our study, only one Pacini corpuscle was found. The Pacinian corpuscle is a low-threshold and

**Table 2** Distribution and type of innervation in AOL and DRL of surgical patients with OA and in cadavers

| Study | n | Patient Type | Histological Methods | Predominant Mechanoreceptor Type | Intra-Ligament Mechanoreceptor Distribution |
|---|---|---|---|---|---|
| Ludwig et al. 2015 | 11 | Surgical, symptomatic OA | Paraffin-sectioning + triple antibody immunofluorescence | Unclassifiable* | Non-significant difference between proximal and distal ends*** |
| Hagert et al. 2012 | 10 | Cadaver, no to mild OA | Paraffin-sectioning + triple antibody immunofluorescence | Ruffini** | Significant difference between proximal and distal ends**** |

*Unclassifiable corpuscles made up a median of 84.4% (interquartile range of 55.0% to 100%) of receptors found across all ligament sample types ($n = 42$).
**No quantitative data available, though author reports that "the Ruffini ending was the predominant mechanoreceptor type, with a greater density in the mobile metacarpal portion of each ligament".
***DRL median difference of 0.0 (interquartile range: 0.0 to 0.5); AOL median difference of 0.045 ($p = 0.907$).
****Nerve endings were significantly closer to the distal metacarpal insertion of each ligament ($p = 0.010$).

rapidly adapting corpuscle, signaling acceleration of motion. This indicates a marked decrease in rapidly adapting mechanoreceptors compared with non-OA patients, which has also been seen in patients with hip OA.[34]

### Significance

Extreme range of motion is primarily detected by mechanoreceptors at the bony insertion of the ligament, where collagenous tissue is more flexible than its stiffer mid-portion.[35] This constitutes the rationale for a protective ligamento-muscular reflex activated during high strain, as demonstrated in the wrist, knee and shoulder.[5,21,36,37] However, in ligaments where mechanoreceptors are evenly dispersed,[19] there is continuous afference regarding joint velocity, angle, position and load. This facilitates fine tuned neuromuscular adaptation during activation, a prerequisite for fine tasks conducted by CMC1. Thus, the even distribution of mechanoreceptors within the CMC1 in patients with OA may correlate with a shift in joint function.

In patients with CMC1 OA, impaired or altered cartilage, subchondral bone, synovium, ligaments, nerves, and periarticular muscles may disturb the joint equilibrium and proprioception.[38] Studies of the human knee after trauma have demonstrated loss of mechanoreceptors causing knee instability,[39] and delayed neuromuscular joint protective reflexes in the hamstring muscles following injury of the anterior cruciate ligament.[40] In the wrist, the scapholunate interosseous ligament is richly innervated by mechanoreceptors.[16] Injury to this ligament results in altered carpal kinematics in both the injured wrist as well as in the contralateral wrist compared with healthy individuals.[41] The study reports changes in the wrist kinematics that were identical bilaterally, suggesting permanent damage to proprioceptive and neuromuscular functions. Similarly in OA, proprioceptive afference conveyed by receptors in ligaments and tendons may be mismatched, causing impaired neuromuscular control and additional disproportional joint activity[42] with subsequent pain, weakness and subluxation.[9]

### Limitations

Limitations to our study include the homogeneity of the population and small sample size. However, our subject distribution represents the common demographics of CMC1 OA.[43,44] Additionally, it is possible that with a larger sample size we may have been able to detect smaller differences between the distal and proximal AOL and DRL. Another limitation was our decision to study the AOL and DRL alone, and not the intermetacarpal, ulnar collateral, dorsal central or posterior oblique ligaments, known to stabilize CMC1.[27,45,46] We examined the AOL and DRL as they have the strongest mean difference in innervation density, and are principal stabilizing ligaments of CMC1.[23,24,47,48] They are accessible with minimal dissection thus avoiding substantial trauma of mechanoreceptors, which would hinder analysis. It would be ethically challenging to sample receptors in the ligaments of patients with healthy CMC1 joints, therefore, our study was limited by a comparison to cadavers with no to mild OA.

## Conclusion

Previous research concerning ligamentous proprioception and our current investigation provide preliminary evidence of altered proprioception in OA, linking biomechanical and inflammatory processes preceding OA.[19,23,24,29,31] Presence of mechanoreceptors may be indicative of a protective ligamento-muscular reflex as found in other joints[5,21,36,37] and warrants further neurophysiological investigations of the presence of a ligamento-muscular reflex in CMC1.

Identification of a unique type and distribution of mechanoreceptors in the CMC1 of symptomatic subjects with OA provides potential diagnostic and prognostic value that will have a significant role in the clinical management of patients with CMC1 OA.

Conflict of Interest
Note

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